Research Article

The effect of level of injury and physical activity on heart rate variability following spinal cord injury

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Objective/Background: To assess frequency domain heart rate variability (HRV) parameters at rest and in response to postural autonomic provocations in individuals with spinal cord injury (SCI) and investigate the autonomic influences on the heart of different physical activities.
Design: Cross-sectional study.
Methods: Ten subjects with complete cervical SCI and fourteen subjects with complete low thoracic SCI were prospectively recruited from the community and further divided in sedentary and physically active groups, the latter defined as regular weekly 4 hour physical activity for the preceding 3 months. Sixteen healthy individuals matched for sex and age were recruited to participate in the control group. The Low Frequency (LF), High Frequency (HF) powers and the LF/HF ratio of HRV were measured from continuous electrocardiogram (ECG) recordings at rest and after sitting using a fast Fourier transformation.
Outcome measures: The LF,HF, and the LF/HF ratio at rest and after sitting.
Results: A significant decrease in all HRV parameters in patients with SCI was found compared to controls. The change in HF, LF and LF/HF following sitting maneuver was significantly greater in controls as compared with the SCI group and greater in subjects with paraplegia as compared to subjects with tetraplegia. Better HRV values and enhanced vagal activity appears to be related to the type of physical activity in active subjects with paraplegia.
Conclusion: In this cohort of subjects spectral parameters of HRV were associated with the level of the injury. Passive standing was associated with higher HRV values in subjects with paraplegia.

Keywords: Cardiovascular disease, spinal cord injury, heart rate variability, sitting maneuver, vagal activity, standing frame

Introduction

As life expectancy increases, cardiovascular disease (CVD) has become one of the primary causes of mortality for individuals with spinal cord injury (SCI).[1–3] Lifestyle changes due to reduced physical activity resulting from paralysis, have a negative effect on the cardiovascular control.[4] In addition, sympathetic-parasympathetic imbalance due to disruption of cardiovascular autonomic pathways, seems to be an important factor that influences CVD risk.[5] Cardiovascular abnormalities, ranging from blood pressure irregularities to increased susceptibility to cardiac arrhythmias, are commonly observed in SCI individuals.[6–9]

The severity of these abnormalities depends on the level of injury (LOI), especially in complete injuries. Patients suffering from complete tetraplegia have intact parasympathetic innervation and intact efferent sympathetic innervation of the heart, but without supraspinal control. As the heart receives sympathetic input from the upper four or five thoracic segments of the spinal cord, injury of the latter leads to variable loss of sympathetic neurons. On the other hand, those with injuries below the midthoracic level have full supraspinal cardiac sympathetic control, but may have altered sympathetic innervation of the vessels below the level of injury.Therefore, patients with complete SCI represent a unique cohort of individuals in relation to the anatomy of the autonomic pathways. The degree of sympathetic isolation depends on the neurological LOI, although autonomic

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dysfunction attributed to physical deconditioning has also been reported in low thoracic injuries.[10]

The Autonomic Standards Assessment Form (ASAF)[11] has been developed recently to complement the current standard American Spinal Injury Association Impairment Scale (AIS) neurological examination.[12] The ASAF includes simple measurements of blood pressure (BP) and heart rate (HR) but does not include a comprehensive assessment of cardiac autonomic modulation. Evaluation of cardiac autonomic modulation by heart rate variability (HRV), a method used for cardiovascular risk assessment in cardiac patients, could improve the predictive and clinical value of autonomic assessment.[13]

Analysis of the variability of heart rate by measuring the beat-to-beat fluctuations in the electrocardiogram (ECG), has been used for assessing of the influence of the autonomic nervous system (ANS) on the heart.[14] Spectral analysis of HRV can reflect the autonomic modulation of the sinoatrial node that affects the firing rate of the heart. Specifically, the high frequency (HF-HRV) 0.15 to 0.4 Hz component reflects cardiac parasympathetic modulation, while the low frequency (LF-HRV) 0.04 to 0.15 Hz component includes both parasympathetic and sympathetic modulations.[15] The LF/HF ratio has been described as a measure of the sympatho-vagal balance of the cardiac autonomic nervous system. In the general population, depressed HRV values have been associated with increased risk of cardiovascular events and cardiac mortality independent of other cardiovascular risk factors.[16]

HRV spectral analysis is a non-invasive assessment method that evaluates autonomic dysfunction following SCI. Ditor *et al.*[17] showed that HRV spectral parameters from 10-minute resting supine electrocardiogram are reproducible when repeated within a two-week period, in individuals with SCI. Recent recommendations suggest that the risk prediction power of autonomic nervous tests increases when quantifying autonomic responses to specific provocations, rather than studying unprovoked baseline autonomic function.[18]

In this study we aimed at investigating HRV parameters during postural autonomic provocations in healthy controls and in narrowly defined SCI groups (male individuals with complete tetraplegia vs male individuals with complete paraplegia below T5 level) and the impact of the LOI and the type of physical activity.

Materials and methods

This study received ethical approval from the Research Ethics Board at University of Patras and all participants gave written informed consent. The investigation conforms to the Declaration of Helsinki.

Study population

SCI individuals living in the community were identified, using the medical records from the SCI rehabilitation centre of the University of Patras. Age matched able-bodied controls were then recruited from posters displayed at the University of Patras.

Inclusion/Exclusion criteria

Male individuals with chronic (more than two years post injury) complete traumatic (AIS A) SCI, aged between 18 and 45 years, in sinus rhythm on ECG, stable clinical condition for more than six months and no current secondary complications that can stimulate sympathetic response, were included in the study. Secondary complications were defined as bladder, bowel and skin problems, spasticity, neuropathic pain, orthostatic hypotension, and autonomic dysreflexia. Individuals with AV block, diabetes mellitus I or II, obesity, heart failure, and those under medication likely to affect the HRV parameters (beta-adrenergic blockers or anti-arrhythmic drugs) were excluded. We did not include individuals with paraplegia at T1 to T5 levels, the region that provides sympathetic innervation to the heart, in view of the anticipated variability in the damage of cardiac sympathetic neurons which may lead to variability in the measured cardiovascular parameters.[19] Male, able-bodied volunteers, aged 18–45 years with no previous medical history and sinus rhythm in ECG, comprised the control group.

Each participant underwent a personal interview in order to obtain baseline demographic data as well as information on engagement in physical activity. This included strength and aerobic exercises for able-bodied individuals and upper extremity exercises, use of standing frame and wheelchair sports for individuals with SCI. Physical activity was defined as regular use of standing frame, upper extremity exercises or participation in wheelchair competitive sports for more than four hours per week, extending over three months or more.[20] The choice to collect data on the use of the standing frame was made because of its potential impact on cardiovascular profiles in these patients,[21] and the existing evidence that orthostatic training can improve conditions, such as orthostatic hypotension and vasovagal episodes,[22,23] conditions associated with autonomic dysfunction and impaired baroreflex sensitivity.[24]

Following the interview, the level and completeness of SCI were determined by a thorough AIS neurological examination conducted by a Physiatrist (AK) specialized in SCI. Individuals with complete SCI were divided into two groups based on the injury level. The tetraplegic SCI group (TSCI) that consisted of individuals with cervical injuries between the C5 and C8 level, and the paraplegic SCI group (PSCI) that consisted of individuals with thoracic injuries between the T6 and the T10 level.

Participants were devided in physically active and sedentary groups according to engagement on physical activities. For the purposes of the analysis the physically active individuals of the PSCI group were further divided into those who participated in wheelchair sports (WS subgroup) and those who regularly used the standing frame (SF subgroup).

ECG acquisition and analysis

All ECG measurements were performed in a quiet and temperature controlled (21–24° C) room between 10:00 and 13:00. All participants were instructed to refrain from caffeine, alcohol, and smoking for two hours before testing. On arrival at the laboratory, subjects were asked to empty their bladder to minimize the effects of bladder distension on sympathetic activity and then rested in the supine position on a bed while resting HR and BP were measured; assistance was given with transfers when necessary.

Following 10 minutes of quiet rest in the supine position, continuous three lead ECGs was initiated using Dantec keypoint G4 (Natus Europe GmbH, Planegg, Germany) with a sampling rate of 5 kHz. Patients remained in the supine position for 420 seconds. This was then followed by a sitting position which was achieved by raising the head of the bed by 90° and lowering the legs from the knee by 90°. The legs were unsupported below the knee. Participants were recorded in this sitting position for another 420 seconds.

The ECG recording was visually checked, and artifacts were eliminated. The time series were constructed using linear interpolation for converting the non-equidistantly sampled RR interval function to equidistantly sampled within five minute windows, and a power spectrum was calculated by Fast Fourier Transformation. The Low Frequency (LF) (0.04 Hz to 0.15 Hz) and High Frequency (HF) (0.15 Hz to 0.40 Hz) powers of the spectrum in absolute values, and the LF/HF ratio were used for the analysis.

The ECG data were exported as a text file to the HRV analysis software (Kubios heart rate variability software version 2.1, Biosignal Analysis and Medical Imaging Group, Department of Physics, University of Kuopio, Finland) for calculation of the spectral parameters of HRV. The analysis was performed according to previously published standards.[15]

Data analysis

Continuous variables are presented with mean and standard deviation (SD). Qualitative variables are presented with absolute and relative frequencies. Kolmogorov-Smirnov test was used to investigate if the normality assumption was satisfied. For the comparison of proportions, chi-square and Fisher's exact tests were used. For the comparison of continuous variables between TSCI, PSCI, and controls, one-way analysis of variance (ANOVA) was used. Differences in changes of LF, HF and LF/HF during the measurements in the supine and sitting position between the three study groups, were evaluated using repeated measures ANOVA. Bonferroni correction was used in case of multiple testing in order to eliminate type I error. All propability (P) values reported are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (version 19.0).

Results

A total of 30 individuals with SCI that were identified fulfilling the inclusion criteria during the initial screening of the medical records, and 24 consented to take part in the study (10 TSCI and 14 PSCI). In the control group, 16 able-bodied volunteers participated out of 24 responders.

Mean demographic data are presented for the three study groups in Table 1. The mean age was 35.5 years (SD = 5.8 years) for the control group, 34.9 years (SD = 5.9 years) for the TSCI group and 36.6 years (SD = 7.4 years) for the PSCI group ($P = 0.808$). The three study groups were also similar in terms of body mass index and smoking habits. The resting BP was significantly lower in the TSCI group as compared with the PSCI group and controls ($P < 0.001$). Resting mean HR was similar across the three groups ($P > 0.05$).

The proportion of engagement in physical activity was 56.3% in the control group, 40% in the TSCI group and 78.6% in PSCI group ($P = 0.152$). In the TSCI group, the physically-active individuals reported only regular upper extremity exercises. In the PSCI group, five physically-active individuals were involved in upper extremity exercises and regular use of standing frame, while six physically-active individuals were involved in upper extremity exercises and regular participation in competitive wheelchair sport activities but no use of standing frame.

Table 1. Characteristics of the three study groups

	Control (N=16)	TSCI (N=10)	PSCI (N=14)	P
Age in years (SD)	35.5 (5.8)	34.9 (5.9)	36.6 (7.4)	0.808*
Years since injury (SD)	(NA)	7.9 (5.5)	12.9 (5.5)	0.039*
Level of injury	(NA)	C5-C8	T6-T10	
BMI (kg/m^2) (SD)	25.5 (2.9)	25.2 (3.3)	25.8 (3.1)	0.889*
BMI status (%)				
Normal	8 (50.0)	6 (60.0)	6 (42.9)	0.710$^+$
Overweight	8 (50.0)	4 (40.0)	8 (57.1)	
Physical activity (%)				
No	7 (43.8)	6 (60.0)	3 (21.4)	0.152$^+$
Yes	9 (56.3)	4 (40.0)	11 (78.6)	
Smoking (%)				
No	10 (62.5)	7 (70.0)	9 (64.3)	>0.999^{++}
Yes	6 (37.5)	3 (30.0)	5 (35.7)	

TSCI: Tetraplegic Spinal Cord Injury; PSCI: Paraplegic Spinal Cord Injury;
BMI: Body Mass Index; NA: Non Applicable
*ANOVA; $^+$Pearson's x^2 test; $^{++}$Fisher's exact test

LF measurements in the supine and the sitting position for the three study groups are presented in Table 2. In the supine position, the LF was significantly higher in the control group, as compared to the TSCI and PSCI groups ($P < 0.001$ and $P = 0.004$ respectively). Additionally, LF in the supine position was higher in the PSCI group, as compared to the TSCI group ($P = 0.002$). In the sitting position, the LF was significantly higher in the control group, as compared to the TSCI and PSCI groups ($P < 0.001$ for both comparisons). Moreover, LF in the sitting position was higher in the PSCI group, as compared with the TSCI group ($P = 0.006$). LF increased significantly from the supine to the sitting position in both the control and the PSCI group, but not in the TSCI group. As indicated from the significant interaction effect, the degree of increase in LF was significantly higher in control and the PSCI group, as compared with the TSCI group and higher in the control group, as compared with the PSCI group ($P < 0.001$).

HF measurements in the supine and the sitting position for the three study groups are presented in Table 3. In the supine position, HF was significantly higher in the control group, as compared with the TSCI and PSCI groups ($P = 0.030$ and $P = 0.006$ respectively). No group differences were found in the sitting position ($P > 0.05$). HF decreased significantly

Table 2. LF measurements for the three study groups

Group	Supine Mean (SD)	Sitting Mean (SD)	Difference Mean (SD)	P**	P$^+$
Control	1083.6 (253.7)	1567.2 (437.9)	483.6 (298.4)	<0.001	<0.001
TSCI	444.5 (134.4)	536.8 (108.4)	92.3 (142.8)	0.177	
PSCI	799.5 (240.7)	1004.0 (305.3)	204.5 (104.5)	0.001	
P* control vs. TSCI	<0.001	<0.001			
P* control vs. PSCI	0.004	<0.001			
P* TSCI vs. PSCI	0.002	0.006			

LF: Low Frequency; TSCI: Tetraplegic Spinal Cord Injury; PSCI: Paraplegic Spinal Cord Injury;
Repeated measurements ANOVA: * P value for group effect;
** P value for change from supine to sitting position; $^+$ Effects reported include differences between the groups in the degree of change.

Table 3. HF measurements for the three study groups

Group	Supine Mean (SD)	Sitting Mean (SD)	Difference Mean (SD)	P**	P$^+$
Control	519.8 (122.5)	315.0 (89.1)	-204.8 (82.4)	<0.001	0.004
TSCI	380.4 (74.7)	296.5 (84.0)	-83.9 (94.0)	0.007	
PSCI	365.0 (158.5)	253.3 (84.7)	-111.7 (104.5)	<0.001	
P* control vs. TSCI	0.030	1.000			
P* control vs. PSCI	0.006	0.175			
P* TSCI vs. PSCI	1.000	0.703			

HF: High Frequency; TSCI: Tetraplegic Spinal Cord Injury; PSCI: Paraplegic Spinal Cord Injury;
Repeated measurements ANOVA: * P value for group effect;
** P value for change from supine to sitting position; $^+$ Effects reported include differences between the groups in the degree of change.

Table 4. LF/HF measurements for the three study groups

Group	Supine Mean (SD)	Sitting Mean (SD)	Difference Mean (SD)	P**	P+
Control	2.1 (0.4)	5.1 (1.0)	3.0 (0.7)	<0.001	<0.001
TSCI	1.2 (0.2)	1.9 (0.6)	0.8 (0.5)	0.003	
PSCI	2.5 (1.0)	4.1 (1.1)	1.6 (1.0)	<0.001	
P* control vs. TSCI	0.002	<0.001			
P* control vs. PSCI	0.448	0.026			
P* TSCI vs. PSCI	<0.001	<0.001			

LF/HF: Low Frequency/High Frequency; TSCI: Tetraplegic Spinal Cord Injury; PSCI: Paraplegic Spinal Cord Injury;
Repeated measurements ANOVA: *P value for group effect;
** P value for change from supine to sitting position; + Effects reported include differences between the groups in the degree of change.

from the supine to the sitting position in all study groups. As indicated from the significant interaction effect, the degree of decrease in HF was significantly higher in control group, as compared with the TSCI and PSCI groups (P = 0.004).

LF/HF measurements in the supine and the sitting position for the three study groups are presented in Table 4. In the supine position, LF/HF was significantly higher in the control group, as compared with the TSCI group (P = 0.002) and higher in the PSCI group, as compared with the TSCI group (P < 0.001). In the sitting position, LF/HF was significantly higher in the control group and in the PSCI group, as compared with the TSCI group (P < 0.001 for both comparisons). Additionally, LF/HF was significantly higher in the control group, as compared with the PSCI group (P = 0.026). LF/HF increased significantly from the supine to the sitting position in all three study groups. The degree of increase in LF/HF was significantly higher in controls, as compared with the TSCI and PSCI groups and higher in the PSCI group, as compared with the TSCI group (P < 0.001).

In the TSCI group, LF and HF values in the supine position were similar in both active and sedentary groups and did not change significantly after sitting (P > 0.05). LF/HF increased significantly in both active (P = 0.008) and sedentary group (P = 0.006) and the degree of change was not different between the two groups (P = 0.757).

Measurements according to physical activity in the PSCI group are presented in Table 5. The SF subgroup had significantly lower mean resting HR compared to the WS subgroup (P = 0.016). In the supine position, LF values were similar between the SF and the WS subgroups (P = 1.000), but the SF subgroup presented significantly higher HF values compared to the WS subgroup (P = 0.022). In the SF subgroup, HF decreased significantly from the supine to the sitting position (P < 0.001), while in the WS subgroup, HF remained unchanged (P = 0.127). The HF decrease for both groups is illustrated in comparison to the control group (fig. 1). The LF/HF increased from the supine to the sitting position in both the SF and the WS subgroup, but the overall increase was higher in the former subgroup (fig. 2).

Discussion

In this study, we analyzed spectral parameters of HRV in subjects with SCI compared with able-bodied controls in supine and sitting positions. Our results showed that both LF and HF parameters of HRV were lower in subjects with SCI compared with able-bodied controls, indicating a decrease in the autonomic cardiac modulation. Furthermore, within SCI individuals, LF and HF were lower in subjects with cervical injuries compared to those with low thoracic injuries. The LF/HF ratio was lower in the subjects with tetraplegia compared to able-bodied controls, but was not significantly different in the subjects with paraplegia. Finally, the difference of LF, HF and LF/HF from supine to sitting position, was higher in able-bodied subjects compared to subjects with paraplegia, and higher in subjects with paraplegia compared to those with tetraplegia. Our findings demonstrated abnormal autonomic cardiovascular regulation after SCI, the severity of which depends on the LOI.

Table 5. Measurements of HR, LF, HF and LF/HF according to physical activity in PSCI subgroups.

		LF (SD)		HF (SD)		LF/HF (SD)	
Subgroup	HR (SD)	Supine	Sitting	Supine	Sitting	Supine	Sitting
WS	72.93 (5.09)	791.8 (306.3)	953.0 (331.1)	281.8 (130.0)	246.5 (109.8)	3.0 (1.1)	4.2 (1.6)
SF	64.13 (4.64)	883.6 (189.7)	1191.2 (233.3)	514.8 (71.0)	284.4 (50.8)	1.7 (0.2)	4.3 (0.9)
P	0.016	1.000	0.581	0.022	1.000	0.065	1.000

HR: Heart Rate; LF: Low Frequency; HF: High Frequency; LF/HF: Low Frequency/High Frequency;
PSCI: Paraplegic Spinal Cord Injury; WS: Wheelchair Sports; SF: Standing Frame
Repeated measurements ANOVA: P value for group effect.

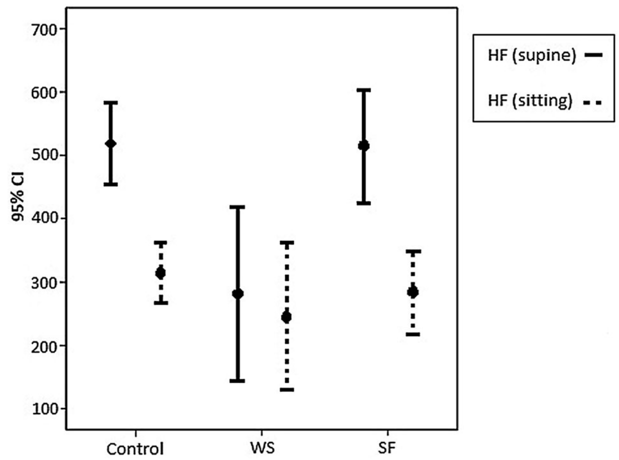

Figure 1. Error bars for High Frequency (HF) measurements in the supine and sitting positions between control group, wheelchair sports (WS) subgroup and standing frame (SF) subgroup.

Previous studies in individuals with SCI have shown conflicting results in regard to the relationship between the spectral components of HRV and the LOI. In subjects with tetraplegia, the LF component has been reported depressed[25–29] or even abolished[30–32] in the absence of noxious stimuli below the LOI, and the HF component has been reported higher,[28,32] similar[29] or lower[25,27,30,31,33] compared to controls. In our study, both components were decreased, but present in the TSCI group. The finding that the LF power is not completely eliminated in subjects following complete cervical SCI is in line with previous observations, showing that part of the low frequency component of HRV is mediated by parasympathetic mechanisms.[34,35] In subjects with paraplegia, Claydon *et al.*[28] reported similar LF and lower HF compared to controls, whereas Rodrigues *et al.*[29] reported lower LF, but no change in the HF values. Both investigators included patients with both complete and incomplete SCI in their sample. Our results are in line with two studies that included only individuals with low paraplegia,[27,30] showing reduction in both components in the PSCI group, and suggesting impaired autonomic modulation even in intact cardiac autonomic innervations.

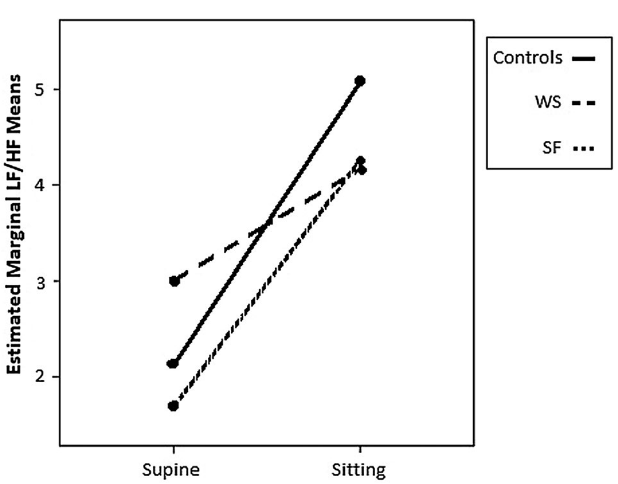

Figure 2. Means for Low Frequency/High Frequency (LF/HF) measurements in the supine and sitting positions between control group, wheelchair sports (WS) subgroup and standing frame (SF) subgroup.

The mechanisms underlying reduced HRV values in subjects with SCI could be explained by the disruption of spinal cord autonomic communication pathways and the additional effect of reduced mobility and reliance on the wheelchair. The observed differencies among individuals with SCI may be related to differencies to the input from the T1–4/5 preganglionic sympathetic neurons from the intermediolateral cell column of the spinal cord. However, cardiac autonomic regulation is also affected by chances of the sympathetic input to the vasculature below the LOI which is present in both TSCI and PSCI.

The reasons for the HRV discrepancies reported in the literature could be attributed to a number of factors affecting data collection. Although the recording conditions seem to have the major impact,[36] there are also other factors such as the combination of different etiologies and the variety of location and severity of SCI. Physical activity status is also a known factor affecting HRV measurements.[37] A study by Zamunér *et al.*[38] that analyzed the differences in HRV between sedentary and active subjects with low paraplegia, reported decreased sympathetic and increased parasympathetic modulation in the active group. Moreover, a recent study by Serra-Ano *et al.*[39] reported reduced variability in sedentary compared to active subjects with paraplegia, as assessed by detrended fluctuation analysis. Both studies defined SCI individuals as active in relation to the time spent participating in wheelchair sports, and no postural autonomic provocations were applied.

Our study aimed at evaluating the effect of different types of physical activity among active SCI individuals, based on previous observations in the general population that orthostatic training can be effective in the prevention of orthostatic hypotension, which is commonly associated with impaired baroreflex.[23,40] Our results showed that the SF subgroup had significantly higher HF values compared to the WS subgroup, indicating enhanced parasympathetic activity which has been shown to restore and protect the cardiovascular system.[41] Furthermore, the wheelchair athletes demonstrated lower mean HF decrease and LF/HF increase while sitting than the individuals with paraplegia who use the standing frame regularly.

The mechanism linking orthostatic training and cardiovascular regulation remains unclear. In the general population, it has been hypothesised that standing training and repetitive orthostatic stress can restore abnormal autonomic reflexes and improve cardiovascular regulation.[42] However, similar improvement in cardiovascular control with the use of standing frame alone, has not been reported in individuals with SCI.[43–45] The significantly higher parasympathetic cardiac modulation in the SF subgroup reflected in HF profiles, requires further research to elucidate the effect of different activities on autonomic dysfunction, vascular compliance and vasomotor tonus. The more brisk response in subjects with paraplegia who regularly used the standing frame compared with the wheelchair athletes, might indicate a possible benefit of the orthostatic stress in improving the cardiac autonomic modulation.

Cardiovascular disease is one of the major causes of death in the SCI population. Cardiac autonomic dysregulation is one of the main risk factors, has specific characteristics based on the LOI, and may be modified with different types of physical activity. Prospective studies are required to assess the impact of exercise programs on cardiovascular risk profiles.

Limitations of the study

Our study has a number of limitations. First, this was a cross-sectional study with small sample size, therefore, caution should be exercised in the interpretation of the results. Second, this study used the AIS to define sensory-motor complete injuries, however, complete injuries based on this assessment do not necessarily correlate with autonomic completeness.[46] Third, information on physical activity in the SCI group was collected as binary parameter, and we did not record the vigor and time spent exercising. Large differences in the volume of exercise may have influenced the results. Fourth, we did not assess arterial stiffness which has been shown to increase in persons with SCI,[47] to improve with exercise,[48] and is known to affect the HRV parameters.[49] Lastly, although we used HRV, we did not assess blood pressure variability that could provide more information about baroreflex sensitivity.

Conclusions

This study confirmed that cardiac autonomic dysfunction which is common following SCI, depends on the LOI and can be assessed by HRV analysis. Short term HRV parameters can provide quantitative measurements of cardiovascular control, they are easy to use in practice and, hence have a potential role in the routine autonomic assessment of individuals with SCI. Moreover, our study showed that regular use of standing frame was related with better HRV profile. Future studies should examine the outcome of different physical activities on the ANS aspects, to enable designing effective exercise programs to reduce cardiovascular morbidity and mortality.

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Disclaimer statements

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